REMARKS

Status of the Claims

Claims 7-9 are pending in this application. In the present Response, claim 6 has been canceled without prejudice to or disclaimer of the subject matter therein. Claim 7 has been amended as described elsewhere herein. Support for this amendment is set forth in the Remarks, below, or can found in the original claims as filed. Thus, no new matter has been added by way of amendment.

Summary of Prosecution

Applicants have disclosed that the CASB7439 transcript is over-expressed in colon tumor, as compared to adjacent normal colon tissue. See Example 1. As stated in their Abstract, Applicants have disclosed methods for utilizing CASB7439 polypeptides and polynucleotides in diagnostics, and vaccines for prophylactic and therapeutic treatment of cancers, particularly colorectal, breast, and lung cancers, autoimmune diseases, and related conditions. One embodiment described in the specification is a method of inducing an immunoresponse to CASB7439 in a human or non-human animal comprising administering a peptide fragment of SEQ ID NO:2 to the human or non-human animal. See the specification, paragraph [0005]. The polypeptide of SEQ ID NO:2 is structurally related to other proteins of the achaete scute family, and is also named "human Achaete Scute homologue 2" (ASCL2 or HASH2) (accession number NP005161 and AAB86993). See paragraph [0088].

Applicants have disclosed that such methods can be used:

> ...for inducing, re-inforcing or modulating an immunological response in a mammal which comprises inoculating the mammal with a fragment or the entire polypeptide or polynucleotide of the invention, adequate to produce antibody and/or T cell immune response for immunoprophylaxis or for therapeutic treatment of cancer, more particularly colorectal cancer, and autoimmune disease and related conditions.

See paragraph [0133] of the specification.

Notwithstanding the foregoing use, Applicants have also disclosed that the methods can be used "to generate antibodies or reagents specific for the polypeptide of the present invention, as diagnostic reagents to detect...genetic or biochemical markers

in blood or tissues that will enable the detection of very early changes along the carcinogenesis pathway will help in determining the best treatment for the patient." See paragraphs [0182]-[183]. Those of skill in the art understand that such "surrogate tumor markers" can be used to diagnose and stage different forms and states of cancer. See paragraph [0183]. For example, one could easily use these markers to compare the expression of a particular gene between a diseased tissue and a normal tissue. See paragraph [0184]. The comparison can be made at the protein level. See paragraph [0188]. Those of skill in the art can also easily detect tumor marker expression levels and subcellular localization by using antibodies to the corresponding protein. See paragraph [0200]. Antibodies for use in the method are easy to make and can be obtained by administering the polypeptides or epitope-bearing fragments to an animal, which may be a non-human animal, using routine protocols. *Id.*

The present application was subject to restriction and the presently examined group of claims were chosen for prosecution. These claims were rejected in the first Office Action mailed 27 Oct 2006 under Section 112, first paragraph, written description, and second paragraph, definiteness over the recitation of the term "CASB7439." The claims were also rejected under Section 112, first paragraph, enablement, over the Office Action's reservations regarding (i) the efficacy of cancer immunotherapy and (ii) the immunogenicity of SEQ ID NO:2 or fragments thereof. Regarding efficacy, the Office Action expressed reservations whether one of skill in the art would be able to use peptide fragments of SEQ ID NO:2 to treat cancer effectively due to unpredictability in the art. With respect to its reservations over the immunogenicity of SEQ ID NO:2, the Office Action explained that "variants of SEQ ID NO:2 may not be expressed on colon cancer cells, to be recognized and lysed by CTLs, because it is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type." Office Action mailed 27 Oct 2006, paragraph spanning pages 10-11.

In their Response dated 15 Feb 2007, Applicants amended the claims to no longer recite "CASB7439." Applicants also drew the Office Action's attention to the lack of any claim limitation reciting efficacious cancer therapy. Applicants explained that the

rejection was reading such a limitation into the claims and that this was legally improper. Applicants also submitted numerous references supporting a conclusion that those of skill in the art would be able to use a peptide fragment of a tumor antigen in a method for inducing an immune response in an animal. With respect to the doubts the Office Action expressed over whether SEQ ID NO:2 is over expressed in cancer cells, Applicants also drew the Office Action's attention to data establishing that SEQ ID NO:2 is (i) immunogenic and (ii) expressed at a high level in colon cancer and at a very low level in normal colon. See the Response dated 15 Feb 2007, citing several examples, Figures 7 and 8, as well as citing Jubb *et al.* (2006) *Oncogene*, 25:3445–3457 (which independently confirms Applicants' findings that neoplastic changes in colon cells are associated with the overexpression of various forms of SEQ ID NO:2).

In the present Final Office Action, the rejection under Section 112, second paragraph has been withdrawn. The Section 112, first paragraph, written description rejection has been maintained, but that rejection is moot in view of Applicants amendment, described herein below. As for the rejection under Section 112, first paragraph, enablement, the reservations related to the expression levels of SEQ ID NO:2 are no longer mentioned. However, the Office Action maintains the rejection on the grounds that Applicants claims are fairly read as methods "of cancer therapy, such as reducing cancer cell growth *in vivo*...," that this claim construction is both fair and legally supportable, and that one could not use fragments or peptides of SEQ ID NO:2 to efficaciously treat cancer or reduce tumor cell growth.

The Office Action's comments are addressed below in the order set forth therein.

The Rejections Under 35 U.S.C. § 112, 1st ¶, Written Description, Should be Withdrawn

Claims 6-9 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. This rejection is respectfully traversed.

The rejection states that the specification does not provide a written description for the genus of molecules recited in the claims, specifically objecting to the clause "...inducing an immunoresponse to ASCL2...," a biological molecule that was well characterized at the time of filing. The art demonstrates that the molecule was well-

characterized: The well-known public database "Online Mendelian Inheritance in Man™," available at http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=601886, provides a full description for ASCL2 (Achaete-Schute Homolog 2; HASH2) based upon three scientific publications, none of which are newer than 1997. This shows that the ASCL2 gene was sufficiently characterized by 1997 such that ordinarily skilled artisans would easily comprehend the molecule described by the term ASCL2. Applicants have drawn the Office Action's attention to binding legal precedent for the principle that a written description rejection is inappropriate where, as here, "the claim terms at issue...are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385 (CAFC 2003). Nonetheless, the rejection has been maintained.

While Applicants are puzzled by the maintenance of the rejection, the recitation of "ASCL2" does not appear necessary to the claim: SEQ ID NO:2 is the published amino acid sequence of human ASCL2, thus any immune response induced by administering a peptide fragment of SEQ ID NO:2 would logically appear to be an immune response to ASCL2. Accordingly, Applicants have removed the term ASCL2 from the pending claims. The rejection is therefore mooted and should be withdrawn.

The Claims Rejections Under 35 U.S.C. § 112, 1st ¶, Should Be Withdrawn

Claims 6-9 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Applicants respectfully traverse.

As the Office Action has stated, an application must teach those of skill in the art to make and use the claimed subject matter without undue experimentation. However, the rejection is clearly founded on the argument that one of skill in the art could not use the claimed methods: The Office Action alleges that Applicants lack enablement for "...using any epitope fragment of SEQ ID NO:2..." (page 3); that "...not any peptides from any cancer antigens would be useful as a vaccine for cancer therapy..." (page 4); that Applicants' claimed method would not be "...effective or useful for therapeutic application" (page 6); and that Kirken *et al.* teaches that "...not any peptides of any tumor antigens are CTL peptides and/or are useful for treating cancer." There is not a

single allegation that it would require undue effort for one of skill in the art to make the claimed subject matter. Rather, the Office Action repeatedly alleges that the claimed subject matter could not be used for cancer therapy to reduce cancer cell growth. The rejection should be withdrawn for two (2) reasons:

(1) The Office Action's claim construction is legally incorrect because it reads in a claim limitation that the recited immune response must cause *in vivo* tumor regression. This legal error has caused the Office Action to select an evidentiary standard for usefulness—efficacious cancer therapy evidenced by tumor regression—that is overly restrictive and unfairly high.

(2) The Office Action has narrowly focused upon whether Applicants have demonstrated tumor regression to the detriment of other uses for the claimed subject matter.

I. The claim construction is legally incorrect.

The rejection construes the claims as if they recite an endpoint of tumor reduction. Applicants have brought this erroneous construction to the attention of the Office, but the claims construction was maintained. See page 9 of the Office Action. For the reader's convenience, Applicants reproduce the claim that the Office Action alleged to contain an endpoint of "tumor reduction." (The claim has since been canceled for the reasons stated above.)

> 6. A method of inducing an immunoresponse to ASCL2 in a human or non-human animal comprising administering a peptide fragment of SEQ ID NO:2 to the human or non-human animal, said peptide fragment comprising an epitope of SEQ ID NO:2.

As can be clearly seen, neither canceled claim 6 nor any of the currently pending claims recite "treating cancer," "cancer treatment," "tumor reduction," or the like.

It is elemental that a rejection must be based upon a correct reading of the claims. Indeed, the MPEP cautions that "Office Action personnel should also be especially careful not to read into a claim unclaimed results, limitations or embodiments of an invention." See MPEP § 2107.02 citing *Carl Zeiss Stiftung v. Renishaw PLC*, 945 F.2d 1173, 20 USPQ2d 1094 (Fed. Cir. 1991); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961). Notwithstanding that Applicants' claims recite neither a step of successfully treating cancer nor an endpoint of tumor reduction, the Office Action has

continued to construe the claims as if they do. See page 9 of the present Office Action. Because this has the effect of importing an element into the claims, the Office Action's claim construction is legally incorrect.

In past communications, Applicants have pointed out the lack of any cancer treatment element in the claims, but the Office Action has replied that the claims *encompass* methods of treating cancer and tumor reduction. In particular, Applicants explained that one could potentially treat cancer using a polypeptide fragment by practicing Applicants' method for inducing an immune response, but it does not logically follow that one must effectively treat cancer to enable Applicants' claimed methods for the induction of an immunoresponse to a polypeptide fragment. See Applicants' Response dated 15 Feb 2007, page 11. Applicants' explanation was deemed non-persuasive and the Office Action maintained that "[t]he claims are reasonably interpreted as a method of cancer therapy, such as reducing cancer cell growth *in vivo*...." See page 9. Applicants disagree because this construction reads a limitation into Applicants' claims that is not present and restricts the enablement analysis to whether this improperly imported limitation is enabled.

In short, the present rejection should be withdrawn because it is based the legally unsupportable construction that the claims require a step of successfully treating cancer or reducing tumor size. This mistaken construction has lead to an improperly restrictive standard for enablement, seen throughout the arguments made in the present Office Action. Applicants reply to each of the Office Action's points in the following pages.

In Section A of the present Office Action, the argument is advanced that one of skill in the art could not use Applicants' method for inducing a therapeutic immune response using any epitope fragment of SEQ ID NO:2 because of, among other things, the unpredictability of cancer immunotherapy. See page 3. This argument is based upon the Office Action's improper claim construction. When this rejection was first made, the Office Action relied upon many scientific publications, almost half of which are from 1995 or earlier: See the first Office Action mailed 27 Oct 2006, citing publications by Smith (1994) *Clin. Immunol.* 41:841-9; Boone (1992) *Adv. Can. Res.*

58:177-210; Ezzell (1995) *J. NIH Res.* 7:46-9; and Spitler (1995) *Cancer Biotherapy* 10:1-3. In response, Applicants pointed out that these references were irrelevant to the inquiry of whether the presently claimed subject matter is enabled because due to their age, they do not represent the views of the skilled artisan relevant to the present filing. The Office Action rejected Applicants' reasoning, arguing that "the cited references however have not been disputed by the art...." See the Office Action mailed 18 Apr 07, page 4. Such a rejection does not address Applicants' point that the references were outdated by Applicants' priority date and do not represent the appropriate state of the art for the present enablement inquiry. As the Office is well aware, the state of the art changes and evolves over time, yet scientific references are not "disputed" simply because they may contain outdated views of the state of the art. Those of skill in the art understand that such statements merely reflect the historical views of the authors.

In Applicants' last Response, the Applicants drew the Office Action's attention to (i) Rosenberg *et al.* (2004) *Nat. Med.* 10:909-915, which reports on cancer studies involving MART-1, gp-100, tyrosinase, TRP-2, NY-ESO-1, MAGE-12, Her2/neu, and telomerase proteins; (ii) Tsuruma (2005) *Vaccines & Antibodies* 5:799-807 reports on studies involving genes highly expressed in colorectal cancer; and (iii) Hoos *et al.* (2007) *J. Immunother.* 30:1-15, which suggests that tumor regression is an inappropriately restrictive endpoint by which to measure usefulness of cancer vaccines. A review of these references reveals that methods involving immunogenic fragments of polypeptides, like those recited in the claims, are considered useful as an adjuvant—or secondary—approach to other therapeutic modalities ranging from chemotherapy to surgical approaches. Moreover, the references teach that immunogenic fragments are useful in non-vaccine settings, such as adoptive immunity. In particular, these references review clinical studies using cancer antigen peptides for immunotherapy, many of which studies were already underway at or around Applicants' priority date. The fact that numerous clinical studies were underway by the mid- to late nineties is strong evidence that those of skill in the art (i) would not have agreed with the Office Action's assessment of immunotherapy and (ii) would certainly be able to use

Applicants' claimed method for inducing an immune response given Applicants' teachings.

In response to Applicants remarks, the rejection once again relies upon Kirkin *et al.* (1998) *APMIS*106:665-79 for its discussion of research related to MAGE-A1 and –A3 peptide induced immunoresponse. The rejection again argues that "Kirkin et al conclude that so far only a few peptides induce response to the antigens in vivo in cancer patients, and resulting in tumor regression (abstract)." To aid the reader, Kirkin's abstract is reproduced here:

> Among the melanoma differentiation antigens, only gp100 has been shown to be a tumor regression antigen. The cancer/testis-specific antigens such as MAGE and PRAME should potentially be highly immunogenic antigens. They contain several potential HLA class I binding epitopes and are present only in the testes, which are not accessible to the cells of the immune system owing to the lack of direct contact with the immune cells and the lack of HLA class I expression on the surface of germ cells. But only two patients have been found who responded to these antigens in vivo, indicating their genuinely low immunogenicity. A comparison of the predicted secondary structures of these two groups of antigens (cancer/testis-specific and differentiation antigens) revealed enrichment of long alpha-helical stretches in the cancer/testis-specific antigens. We hypothesize that such highly organized stable structures could, first, reduce denaturation of the protein and, thus, ubiquitinylation as a degradation signal, and, second, diminish the efficiency of the protein unfolding - a necessary step in the proteolytic cleavage by proteasomes. High structural stability could therefore be responsible for the low immunogenicity of these proteins. <u>In this case, modifications decreasing the stability of these proteins might be a means of improving the immune response to these potentially therapeutically useful antigens.</u>

(Emphasis added.) Contrary to the Office Action's reading, Kirkin *et al.* actually supports a conclusion that those of skill in the art considered a peptide approach viable even in 1998. More specifically, the final sentence of the abstract demonstrates that even by 1998 the skilled artisan not only knew how to use such antigens, but also had a view as to how to improve them such that they would be therapeutically useful. Indeed, as discussed above, by the time of Kirkin *et al.* the first clinical trials were <u>already under way</u>. See page 666 of Kirkin *et al.* Applicants are puzzled that the Office Action argues that by 1998 one of skill in the art would not understand how to use peptides and

fragments of cancer antigens given that clinical trials were already under way by that time.

Applicants pointed out in their last Response that Kirkin *et al.* actually supports a conclusion that those of skill in the art understood how to use fragments and peptides of cancer antigens and also provided additional references to further support this conclusion. In addition, Applicants submitted Marchand *et al.* (1999) *Int. J. Cancer* 80:219-230, which states in its abstract:

> Thirty-nine tumor-bearing patients with metastatic melanoma were treated with 3 subcutaneous injections of the MAGE-3.A1 peptide at monthly intervals. No significant toxicity was observed. Of the 25 patients who received the complete treatment, 7 displayed significant tumor regressions. All but one of these regressions involved cutaneous metastases. Three regressions were complete and 2 of these led to a disease-free state, which persisted for more than 2 years after the beginning of treatment. No evidence for a cytolytic T lymphocyte (CTL) response was found in the blood of the 4 patients who were analyzed, including 2 who displayed complete tumor regression. Our results suggest that injection of the MAGE-3.A1 peptide induced tumor regression in a significant number of the patients, even though no massive CTL response was produced.

Kirkin *et al.* do not support the rejection.

The Office Action now concedes that "a peptide approach is viable," but argues that "not any peptides of any tumor antigens are CTL peptides and/or are useful for treating cancer." See page 6 of the Office Action. However, as fully explained above, the claims lack any limitation to cancer treatment and this reasoning, based on an improper claim construction, does not support the rejection.

As mentioned above, Applicants submitted Marchand *et al.* for support. In Section C of the present Office Action, it is alleged that "Marchand *et al.* used the same MAGE-3 peptide taught by Kirkin *et al.*, the only effective peptide among identifiable MAGE-1, MAGE2 and MAGE-3, MAGE-4, MAGE-6 CTL peptides as taught by Kirkin *et al.*, for treating melanoma." This statement is scientifically misleading. Marchand *et al.* selected one specific peptide based on their published 1995 findings that peptide of MAGE were efficacious against melanoma. This does not mean that the chosen peptide is the only possible efficacious peptide, and the Office Action does not demonstrate that other peptides were tried by Marchand *et al.* and rejected as

inoperative. Indeed, Kirkin *et al.* reviewed more than one effective peptide among the MAGE peptides:

> Two antigenic epitopes of MAGE-A1...have been identified. For MAGE-A2 protein two HLA-A2-binding peptides...have recently been shown to induce the formation of CTL in transgenic mice able to kill MAGE-A2-expressing cells in an HLA-A2-restricted manner. For the MAGE-A3 prteln, four epitopes have been identified: one recognized by HLA-A1-restricted CTL clones of patient MZ2...and three others based on the ability of peptides predicted by known HLA class....

Kirkin *et al.*, page 666. As regards efficacy, Kirkin *et al.* did note at the time of publication that "...so far only one patient has shown an immune response to this group of antigens (patient MZ2), suggesting an extremely low immunogenicity of the MAGE antigens," but greater success was reported in the subsequent publication by Marchand *et al.*, which revealed "tumor regression in a significant number of the patients, even though no massive CTL response was produced." Taken together, these two references support a conclusion that those of skill in the art understand how to use Applicants' claimed method without undue experimentation for a utility such as Immunotherapy.

As stated previously, Applicants cited Rosenberg *et al.* for support in their last Response. The Office Action now refers to a section of Rosenberg *et al.* that questions whether *in vitro* assays can be validated as surrogate endpoints of a clinical response for efficacious cancer treatment. See page 5 of the present Office Action. But this section is not relevant to the appropriate enablement inquiry, i.e., whether one of skill in the art could use fragments or peptides of SEQ ID NO:2 in the claimed methods for inducing an Immunoresponse. Rather, this section of Rosenberg *et al.* is relevant only to whether one of skill in the art could predict the clinical outcome of an immunotherapy based upon *in vitro* assays. Applicants claim only methods of inducing an immunoresponse, there is no required clinical endpoint. Thus, this section of Rosenberg *et al.* is irrelevant to the enablement of these claims.

The Office Action also alleges that Table 2 of Rosenberg *et al.* shows that a small proportion of peptides selected from several cancer antigens produce an effective clinical response in patients. Again, this is not relevant to the properly formulated

enablement inquiry. Moreover, this may not have been surprising—the peptides set forth in Table 2 of Rosenberg *et al.* are HLA restricted and nothing in Rosenberg *et al.* shows that all of the non-responding patients tested had the proper HLA type to even mount a response. In any case, Rosenberg *et al.* also explain that in their view the low levels of clinical response may be alleviated by the following actions:

> Increased numbers of T cells with higher avidity are required *in vivo* and exploration of improved adjuvants such as new toll-like receptor agonists to activate innate immunity, the use of agonistic anti-4-1BB antibodies to stimulate CD8+ cells or the administration of homeostatic cytokines such as IL-15 require study.

But Applicants' specification already teaches the use of improved adjuvants, including those with toll-like receptor agonists:

> [0138] According to another embodiment, the pharmaceutical/immunogenic compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or antigen presenting cell (APC) compositions of this invention.
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> . . . .
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> [0139] Within certain embodiments of the invention, the adjuvant composition may be one that induces an immune response predominantly of the Th1 type.
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> . . . .
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> [0140] Certain adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, including 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt.

See the specification, paragraphs [0138]-[0140]. As is presently known, monophosphoryl lipid A is a toll-like receptor agonist that stimulates innate immune responses. Rosenberg *et al.* is therefore in agreement with Applicants' guidance for how to use fragments and peptides of tumor antigens. Thus, Rosenberg *et al.* supports a conclusion that one of skill in the art would understand how to use Applicants' claimed method.

As mentioned above, Applicants also submitted Tsuruma (2005) *Vaccines & Antibodies* 5:799-807 for support. The Office Action alleges that Tsuruma supports its conclusion regarding the inoperability of immunotherapy because Tsuruma mentions

escape of cancer cells and states that there are insufficient reports of substantial rate of tumor regression. Applicants disagree. Tsuruma explains that cancer cell escape could be countered by using a cocktail of peptides, by use of robust adjuvants (such as those taught by Applicants), or by postoperative adjuvant therapy (i.e., immunotherapy as a therapy secondary to surgery) or as a first-line therapy immediately after recurrence. And although Tsuruma states that there are insufficient reports of tumor regression, it prefaces this statement by noting that "...peptide vaccine therapy, has a large body of preclinical evidence supporting its rationale." See Tsuruma, page 805, first column, last full paragraph, first sentence. Tsuruma cites a scientific report by Letsch *et al.* demonstrating that such an adjuvant peptide vaccination after resection induced a prolonged relapse-free interval in melanoma patients. See Tsuruma, page 805, second column, third full paragraph. Thus, Tsuruma provides much evidence showing that those of skill in the art understand how to use peptides for vaccine therapy. Even if the correct enablement inquiry turned on the question of whether one of skill in the art could use Applicants' claimed method for immunotherapy (which it does not), nothing more would be required to demonstrate enablement. See *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

As mentioned on page 9 herein above, Applicants have also cited Hoos *et al.* (2007) *J. Immunother.* 30:1-15 for the premise that tumor regression is an inappropriately restrictive endpoint by which to measure the outcome of a cancer vaccine trial and that therefore, even if Applicants claims recited a cancer treatment step, this would be an inappropriate endpoint by which measure enablement. The Office Action brushes this reference aside, arguing that it is not germane. This is not so. The Office Action has focused on the narrow question of whether Applicants have demonstrated that their claimed method results in tumor regression. Hoos *et al.* stands for the principle that tumor regression is an inappropriately restrictive endpoint by which to assess an immunotherapeutic. Thus, Hoos *et al.* is highly relevant evidence that shows that the endpoint selected by the Office Action is not appropriate for judging the enablement of Applicants claimed methods for inducing an immune response.

Next, the Office Action states

> Concerning the response's comment that methods involving immunogenic fragments of polypeptides are useful as an adjuvant to other therapeutic modalities, and that immunogenic fragments are useful in non-vaccine settings, such as adoptive immunity, the response argues limitation not the claims.

See page 5 of the present Office Action (emphasis added). Applicants representative does not know what this means. Clarification is requested.

The Office Action then argues that

> Further, there is no indication that the claimed peptides actually have any adjuvant effects, enhancing the effectiveness of other therapeutic modalities, such as conventional chemotherapy.

Essentially, the Office Action is requiring that Applicants demonstrate efficacious cancer treatment, but for the reasons already stated, this goes far beyond the legally supportable standard for enablement of a method for inducing an immunoresponse.

In part B of the present Office Action, White *et al.* is discussed. White *et al.* was first mentioned in the Office Action dated mailed 27 Oct 2006 for the proposition that immunotherapy is unpredictable because of the possibility of antigen internalization or down-regulation due to repeat dosing. Applicants replied by emphasizing that their claims contain no requirement that the recited method successfully treats cancer or includes repeat dosing steps and that the reference is irrelevant to whether one could induce an immunoresponse to ASCL2 by administering a peptide fragment of SEQ ID NO:2.

In the present Office Action, it is now stated (with certainty) that

> ...due to internalization or down-regulation of the antigen or the MHC molecules, the antibodies or the T cells would not be able to recognize the target cancer cells, and thus would not be effective or useful for therapeutic application.

This statement is speculative and under the Rules cannot be relied upon to support the rejection without an affidavit. Moreover, it is still irrelevant to Applicants' claimed method, which includes neither a clinical efficacy endpoint nor a repeat dosing step.

Section C of the Office Action was discussed on page 11 herein above.

In Section D of the present Office Action, Gaiger (2000) *Blood* 96:1480-9 is discussed. Gaiger was first cited in the Office Action dated 27 Oct 2006 for its report that WT-1 peptides, although immunogenic, did not show any effect on WT-1 cancer growth *in vivo*. Applicants submitted a responsive scientific reference showing that other researchers have demonstrated that peptide fragments of WT-1 are immunogenic and do affect cancer growth *in vivo*. See Oka *et al.* (2004) *PNAS* 101:13885-13890. The Office Action now responds that Oka *et al.* is not found to be persuasive because the peptide used by Oka *et al.* is different from that used by Gaiger *et al.* Specifically, the Office Action states that:

> [r]eviewing the teaching of Oka et al and Gaiger et al thus confirms that not any CTL peptides of tumor antigen, even those inducing specific tumor cell lysis in vitro, and antibodies in vivo, in cancer patients, are capable of reducing cell growth of cancer cells in a patient.

Applicants' representative admits to some confusion over this statement: The first Office Action stated that WT-1 peptides were not efficacious for tumor regression based upon Gaiger *et al.* Applicants submitted a reference rebutting Gaiger *et al.* by showing that WT-1 peptides can induce an immune response efficacious for tumor regression. Now the Office Action replies that Oka *et al.* is irrelevant because they used peptides different from Gaiger *et al.* Applicants do not agree; Oka *et al.* is relevant to rebut the Office Action's reliance on Gaiger *et al.*

Moreover, both Gaiger *et al.* and Oka *et al.* show that peptides of WT-1 are immunogenic. By analogy, both references support a conclusion that the skilled person could use Applicants method for inducing an immune response to peptides and fragments of SEQ ID NO:2. Because Applicants claims do not recite a tumor regression endpoint, this is all that must established. And Applicants have done this. In Applicants' specification, the Examples present *in vitro* data showing that several peptides which overlap the epitope of SEQ ID NO:25 are specifically recognized by CD4+T cells. See Example 10, "CASB7439 Specific Cellular Immune Response," especially paragraph [0365] of the specification. Cells were assayed for proliferation (3H-Thy) as well as IFN-γ. See paragraph [0360] of the specification. This evidence

supports a conclusion that the fragments recited in the claimed methods can be used to induce a CD4+ immunoresponse, as assayed *in vitro* by cellular proliferation as well as IFN-γ response.

On the presumption that the Office Action may be arguing by analogy (relying on Gaiger *et al.*) that if (I) not every possible peptide or fragment of a cancer antigen would be immunogenic and therapeutic then (ii) not every possible fragment or peptide of SEQ ID NO:2 would be immunogenic, Applicants remind the Office Action that not every possible embodiment must be operative in order to satisfy the statutory standard. In any case, Applicants have amended the independent claim to recite

> A method of inducing an immunoresponse in a human or non-human animal comprising administering a peptide fragment of SEQ ID NO:2 to the human or non-human animal, wherein the peptide fragment comprises an epitope of SEQ ID NO:2 selected from the group consisting of SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, and 33.

The amendment is (I) supported by the original claims and (ii) done only for purposes of reducing issues on review (a review made necessary by the Office Action's insistence that the claims can legally be construed to require an efficacious therapeutic outcome). Applicants reserve the right to file continuation applications claiming the full genus to which they are entitled.

In Section E, the Office Action again states that Hoos *et al.* is not relevant to the predictability of cancer immunotherapy. Applicants have more fully responded to this argument herein above and reiterate those remarks.

The Office Action goes on to state

> [T]he scope of the claimed invention is reasonably interpreted as a method for treating cancer....
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> ....
>
> There is no evidence, nor one can predict that any epitope of SEQ ID NO:2, including SEQ ID NO:25 of the claimed invention could be successfully used for treating cancer, such as reducing cancer cell growth, in view of the teaching of Smith et al, White et al, Kirkin et al, Gaiger et al, Ezzell et all, Sptiler et al, all of record.

Applicants have discussed each of the references mentioned in this sentence more fully above. Moreover, Applicants remind the reader that Applicants claims do not recite a cancer treatment endpoint. The Office Action's claim construction is ill-founded and, as a result, the enablement inquiry carried out over the last several Actions is flawed. Applicants respectfully request that examination be reopened so that the claims can be analyzed for whether or not the skilled person could use Applicants claimed methods to induce an immune response to SEQ ID NO:2.

In Section F of the Office Action argues that Applicants' claims encompass a genus of peptides and fragments for inducing an immunoresponse to SEQ ID NO:2 and that Applicants have disclosed data showing the immungenicity some of these peptides, but that "...one cannot extrapolate from these few CTL peptide to the encompassed genus of epitopes of SEQ ID NO:2 that can induce CTL response, especially *in vivo* in a cancer patient...because only a minority of peptide fragments of a proteins are CTL epitopes in view of the teaching of Roitt *et al.* (1998) (*Immunology*, 4th ed., Mosby, London, p. 7.7-7.8)." The Office Action seems to suggest that the skilled person would expect any possible peptide or fragment of SEQ ID NO:2 to induce a CTL immune response in a cancer patient. This is not the case. The skilled person is well aware of teachings like those in Roitt *et al.* and would understand that not every possible fragment of a polypeptide will induce a CTL response, especially *in vivo*. The skilled person would routinely do just what Applicants have done in their examples: Predict epitopes, synthesize peptides comprising these epitopes, and test them. The skilled person would not consider this level of experimentation undue.

Moreover, Applicants have provided detailed guidance and several working examples of immunogenic epitopes, peptides, and fragments, as set forth in their Response filed 15 Feb 2007, pages 13-14. The Office Action argues in response that this guidance clearly cannot be extrapolated to the genus of the claims in view of "...peptide 21, although [it] induces CTLs recognizing the peptide, said CTLs do not recognize full length SEQ ID NO:2." Applicants note that this is only one of the tested peptides; other peptides not only induce a CTL response, but also produce CTLs that

are capable of recognizing full length recombinant SEQ ID NO:2. See Example 10, Donor #2 and Donor #3. In any case, the Office Action appears to reason that a CTL response is the only useful immunogenic response, likely because it has construed the claims to be limited to methods for inducing an immunoresponse to SEQ ID NO:2 capable of causing tumor regression via a cytotoxic lymphocyte response. But there are other uses for methods of inducing an immunoresponse to SEQ ID NO:2, such as generating antibodies. Some of these uses are detailed on pages 3-4, herein above.

The Office Action also argues that it is unpredictable whether antibodies raised by Applicants' claimed method would bind to full length SEQ ID NO:2 in three dimensional structure. Applicants disclosure rebuts this argument because the examples already disclose antibodies raised to peptides of SEQ ID NO:2 that bind to full-length SEQ ID NO:2.

The Office Action next argues that

> ...screening assays do not enable the claimed invention because the court found in *Rochester v. Searle*, 358 F.3d 916, Fed Cir, 2004, that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

This point is poorly taken: The rule of *Rochester v. Searle* relates only to written description, not enablement. Applicants' representative is unclear as to what point the Office Action is making. However, to the extent that one of skill in the art may have to do some screening to use Applicants' claimed methods, such screening is not undue. *See, e.g., In re Wands*, 8 USPQ2d 1400 (Fed Cir 1988)(a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed). Applicants have provided sufficient guidance regarding which regions of SEQ ID NO:2 are immunogenic. See the Examples and specification, particularly as relates to SEQ ID NOs:16-33. For purposes of further examination, Applicants draw the Office Action's attention to the amendment to the independent claim, which thus narrows the present issue to fragments comprising the epitopes of SEQ ID NOs:16-33.

In Section 2, the present Office Action argues that it has not misconstrued the claims, stating:

> The claims are reasonably interpreted as a method for treating cancer, such as reducing cancer cell growth *in vivo*, via induction of an immunoresponse, using any peptide epitope of SEQ ID NO:2, or the peptide of SEQ ID NO:25.

Applicants have fully addressed this issue herein above, particularly on pages 7-8.

In Section 2, the Office Action also challenges whether those of skill in the art could use the peptides and fragments of SEQ ID NO:2 in conjunction with a fusion partner or adjuvant on the ground that "[t]here is no indication that the addition of fusion partner or an adjuvant would render any peptide fragments of SEQ ID NO:2 a CTL epitope, or inducing antibodies that would recognize SEQ ID NO:2 on a cell surface in a human or a non-human animal...." This statement is puzzling to Applicants' representative because the immune-enhancing properties of carrier proteins, fusion proteins, and adjuvants are well-known in the art. Applicants' specification contains ample guidance on this subject matter. Further, it is well-established that an Applicant need not teach or exemplify that which is well-known and/or scientifically accepted.

In this Section, the Office Action also states that one could not predict that SEQ ID NO:25 would be recognized by CD4+T cells because SEQ ID NO:25 is only 9 amino acids and CD4+T cells typically bind longer peptides. However, Applicants draw the reader's attention to the transitional claim language "comprising" that modifies the term "an epitope of SEQ ID NO:2." Thus, the claim does not exclude fragments or peptides longer than the epitopes of SEQ ID NOs:16-33.

In this Section, the Office Action responds to Applicants' submission of Jubb *et al.* (2006) *Oncogene,* 25:3445–3457. Jubb *et al.* is titled "Achaete-scute like 2 (ASCL2) is a target of Wnt signalling and is upregulated in intestinal neoplasia." Applicants submitted Jubb *et al.* to help allay the Office's concerns over whether ASCL2 was overexpressed in tumors and cancer cells. The present Office Action states that Jubb *et al.* is nonpersuasive because "[t]he encompassed genus of ASCL2 variant are not

limited to the mouse variants." Applicants' representative is baffled, because Jubb *et al.* demonstrate that ASCL2 is upregulated in human intestinal neoplasms (as well as mouse). In any case, Applicants have mooted this point of rejection by amending the claim to no longer recite the term "ASCL2."

The Office Action also contends that the enablement standard relied upon in the present rejection does not inappropriately parallel the regulatory safety standards for drug approval. Specifically, the Office Action states that "A successful cancer treatment, such as reducing cancer cell growth in a human, does not require the same degree as that of clinical trials." Applicants' representative is unable to distinguish the difference between "successful cancer treatment" as selected by the Office Action and "successful tumor regression," the most rigorous of the clinical trial outcomes discussed in any one of the references discussed herein above. The standards are essentially the same and are inappropriate for judging enablement of claims drawn to methods of inducing an immune response.

II. The improper claim construction allows the enablement analysis to overlook *bona fide* uses for Applicants' claimed method for inducing an immunoresponse

In past Responses, Applicants have drawn attention to the incorrect claim construction used in each of the Office Actions, and how this construction forces the enablement analysis to narrowly focus on whether Applicants have demonstrated tumor regression. Despite Applicants' efforts, the incorrect claim construction has been maintained and the focus of the rejections has remained on whether or not Applicants have demonstrated that their method efficaciously treats cancer or causes tumor regression. But this narrow focus overlooks other *bona fide* uses for the presently claimed methods. Applicants described these uses in great detail in their disclosure. Applicants' representative has summarized them in the paragraph spanning pages 3-4 of the present Response. These uses have received no examination due to the Office Action's improper claim construction. The present rejection should be withdrawn and the finality of the present Office Action should be lifted so that complete examination

can take place (complete examination is required under the Compact Prosecution Rule, MPEP § 2106(II).

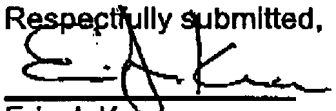
CONCLUSION

In view of the remarks herein above, Applicants respectfully submit that the rejection of claims 7-9 is overcome. The Examiner is respectfully requested to withdraw the rejections and allow claims 7-9. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of further prosecution. The amendments were not made earlier because applicant earnestly believes that the specification is enabling for the breadth of the claims as drafted. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,



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